## REMARKS

Applicant submits this amendment to address the issues raised in the Office Action mailed January 4, 2007. Claims 1-60 are pending in the application. Claims 16-60 are presently withdrawn from consideration pursuant to the Restriction Requirement mailed March 7, 2000, and in view of the Response filed June 2, 2000. Thus, claims 1-15 are currently under consideration. Applicants respond to the rejections in paragraphs numbered to correspond to the Office Action.

1-2. Applicants confirm that claims 1-15 are pending.

3-4. Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph because the claims do not recite the specific amino acid sequence of the mutant *Herpesviridae* thymidine kinase. This allegedly makes it difficult to determine the specific positions where the mutations occur.

Applicant previously argued that the specification adequately supports the locations of the mutations and they need not be specifically recited in the claims. The mutations are described in relation to the DRH and Q substrate binding domains which in turn are well defined as discussed below. Regarding the Q substrate binding domain, the specification clearly indicates at page 83, Example 10, that the codons representing residues 112-132 (second line from end) are the relevant positions. This is also described at page 18, lines 6-7. However, to advance prosecution, claim 1 (and claims 3-15 depending thereon) has been amended to recite the amino acid sequence and specific positions of the mutations.

Regarding the DRH nucleoside binding site, applicants previously argued this site is known in the art, as described, for example, in Black, M.E., *Biochemistry* 32:11618-11626 (1993). Thus, one of skill would be familiar with the meaning and location of a DRH nucleoside binding site. As evidence, applicants previously drew the Examiner's attention to Wu, C.-C. et al., Biochem. J. 379:795-803 (2004), in which the term "DRH" is also employed (page 797, "Results") with reference back to the Black *Biochemistry* 32:11618 publication (reference 32 in Wu). However, to advance prosecution, claim 2 is amended to recite, "wherein said DRH binding site consists of Asp at position 392, Arg at position 393, and His at position 394 of the amino acid sequence encoded by SEQ ID NO:1." No new matter is added, because one of skill in

the art will be familiar with the location of the DRH binding site recited in the claim, and with the genetic code, in which the corresponding nucleotides in SEQ ID NO:1 can be mutated based on the location of the DRH binding site and the limitations of claim 2. Reconsideration and withdrawal of this rejection are respectfully requested.

5-6. Claims 1-15 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action states that the specification does not provide a written description of a specific nucleotide sequence encoding a specific amino acid sequence of mutant *Herpesviridae* thymidine kinases that have mutations in Q substrate domain where the mutations result in thymidine kinase that has any increase of any biological activity or ability to phosphorylate any nucleoside analogue. The Office Action concludes that one skilled in the art cannot visualize or recognize the identity of the members of the claimed genus.

Applicants previously argued that as described at page 84, lines 16-20, several hundred TK positive clones were sequenced with amino acid substitutions spanning the 20 amino acid sequence (residues 112-132, see page 83, last paragraph). Lysates from these mutants were assayed for the ability to phosphorylate thymidine, acyclovir and ganciclovir, and mutation within the Q substrate binding domain altered substrate specificity.

In order to reflect the literal language of the specification in compliance with the written description requirements, applicants previously amended claim 1. However, the Examiner has maintained the rejection, and stated that "one skilled in the art cannot visualize or recognize the identity of the members of the claimed genus." (Page 3, lines 32-33.)

Applicants submit that they are not required to recite in the specification information readily available to those skilled in the art. Applicants cite to the recent Federal Circuit decision *Falkner v. Inglis*, Slip Op. 05-1324 (May 26, 2006) which clarified the written description law as it pertains to biological molecules. The court held that,

> (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice

> of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

The court further stated that recitation of known structure is not required, citing *Capon v. Eshlar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) and distinguishing *Eli Lilly*. The court also noted that "the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification." (*Falkner*, Slip. Op. at 17).

The nucleotide sequence for the genus of *Herpesviridae* thymidine kinase is disclosed in the specification as SEQ ID NO. 1, and generation of sequences with mutations in the Q substrate region is described in detail in Example 10 at pages 76-78. Claim 1 as amended recites that the mutations are found in a very specific region, encoding just twenty-one amino acid residues at positions 112-132.

One basis for the invention is the concept that modification in the Q substrate binding domain yields tk mutants having altered substrate specificity. The invention directs those of skill to focus on the Q substrate binding domain in order to alter substrate specificity of tk. In particular, single amino acid changes within amino acid positions 112-132 had altered substrate specificity (page 77, line 33 to page 78, line 3).

The genetic code is so well known that there is no need to disclose it in patent applications. One of skill can routinely mutate a codon to achieve an altered amino acid at any of positions 112-132, then assay the mutated TK for altered substrate specificity. Writing out the possible altered amino acids is not necessary, as there is a finite set of twenty amino acids. The claims encompass a closed set of sequences, not an unlimited range that one of skill cannot envision. Applicants therefore urge that one skilled can visualize or recognize the identity of the members of the claimed genus.

Reconsideration and withdrawal of this rejection are respectfully requested.

7. Claims 2, 4, 5 and 7 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Reconsideration and withdrawal of this rejection are respectfully requested.

In the previous Office Action, the Examiner cited the Wands factors, *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988).

Applicants argued that one of ordinary skill in the art can construct and use nucleic acid molecules, for example, as described in the specification at pages 83-84 (Example 10), and that such tests would not constitute "undue" experimentation within the scope of *Wands*, as discussed in detail below.

The inventors have, for the first time, produced TK mutants with alterations in the Q substrate binding domain. Applicants applied this information to the eight *Wands* factors, and argued that one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

The Examiner states that working examples are not provided for how to make the claimed polynucleotides without undue experimentation. Applicants disagree with the Examiner's statement that one of skill would have to "screen, search, and assay" for a polynucleotide having the claimed characteristics. There are screening and assay steps after the mutant sequences are expressed, but these are routine in the art, as discussed in detail in the previous response.

The Examiner has provided no art-based evidence that the experimentation is outside the realm of routine experimentation. One factor in meeting the enablement requirement is predictability. The techniques required here are routine in the art, and the assays provide objective results, i.e., "altered substrate specificity." Another factor is amount of experimentation. Wands permit a significant degree of experimentation if it is routine. In these types of experiments the expectation is that most of the variants generated will yield negative results. This is based on the fact that most mutations lead to a loss or ablation of enzyme activity. This is particularly true when more than one substitution is being introduced. Therefore, the expectation is that hundreds of mutations need to be tested. Here, the repetitive nature of the expression and testing for substrate specificity makes up for the possible need to assay many clones, by analogy to Wands.

8-9. Claims 1, 3, 6 and 8-11 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Munir et al., *J. Biol. Chem.* 267:6584-89 (1992) in view of Graham et al., *GenBank Accession No.* X03764 (Sept. 12, 1993); Kit et al., *GenBank Accession No.* X01712 J02225 (Sept. 12, 1993); Drake et al., *Antiviral Res.* 35:177-85 (1997); Waldman et al., *J. Biol. Chem.* 258:11571-75 (1983); Munch-Petersen et al., *J.*

*Biol. Chem.* 266:9032-38 (1991); Balasubramaniam et al., *J. Gen. Virol.* 71:2979-87 (1990); Brown et al., *Nat. Struct. Biol.* 2:876-81 (1995); and Donarian et al., *Gene Therapy* 2:235-44 (1995).

As applicants argued in the previous response, until the experiment was performed and the resulting thymidine kinase mutants assayed, one of skill, reading the references without benefit of hindsight based on applicant's teaching, would not have had the requisite expectation of success. The other references fail to remedy the deficiencies. The particular codons selected for random mutagenesis do not comprise the DRH binding domain. The obvious to try standard does not apply because the codon chosen for mutagenesis are not part of the DRH (site 3) conserved motif identified by Balasubramaniam et al. (1990). Likewise, Brown does not note the codons selected for mutagenesis except for that encoding A168. Furthermore, it is the combination of amino acid substitutions and not the function of a single amino acid mutation that results in significant substrate specificity change. Brown et al. (1995) indicate that an A168T mutation leads to a loss in turnover, not a change in substrate specificity. This is an important distinction. Indeed, a loss in turnover rate suggests that A168 should be kept unchanged and not subjected to mutagenesis.

10. Claims 12-15 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Esandi et al., *Gene Ther* 4:280-87 (1997) in view of Munir, Graham, Kit, and Deonarian.

The Examiner states that the arguments filed on May 30, 2006 were considered, but maintains that it would have been obvious for one of ordinary skill to make an expression vector comprising a promoter operably linked to the claimed nucleic acid encoding the claimed *Herpesviridae* thymidine kinase by inserting the mutated DNA encoding mutant thymidine kinase into the expression vector of Esandi et al. "in order to express thymidine kinase mutants in cancer cells of specific tissue origin which is expected to be effective in the treatment of cancer when these mutants are used in gene therapy as taught by Donarian et al." (Office Action page 7, lines 4-7).

The Examiner's suggestion to insert the mutated DNA into the expression vector of Esandi et al. may rise to the level of "obvious to try" but fails to meet the "expectation of success" standard required for an obviousness rejection. In particular, the Examiner

states that there is an expectation of effectiveness. However, the random mutagenesis method of Munir fails to teach the codons to be mutated in order to achieve applicant's claimed invention, which is an isolated nucleic acid molecule in which the at least one mutation in the Q substrate domain alters the substrate specificity of the thymidine kinase. Until the experiment was performed and the resulting thymidine kinase mutants assayed, one of skill, reading the references without benefit of hindsight based on applicant's teaching, would not have had the requisite expectation of success. The other references fail to remedy the deficiencies. Reconsideration and withdrawal of this rejection are respectfully requested.

If additional fees are believed necessary, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

In view of the above claim amendments and remarks, Applicant submits that the claims are now in condition for allowance and requests that the Examiner issue a Notice to that effect.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 757-8122.

Respectfully submitted,
Margaret E. Black
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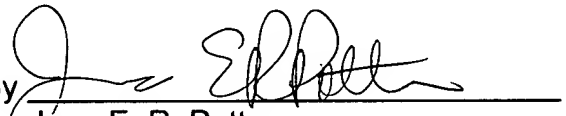
By 
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